

# PATENT SPECIFICATION

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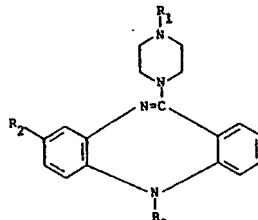
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## (54) DIBENZO[b,e][1,4]DIAZEPINES

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

5 The present invention relates to dibenzo[b,e][1,4]diazepines.  
 The present invention provides compounds of formula I,

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wherein

10 R<sub>1</sub> is hydrogen, alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 2 to 4 carbon atoms, or alkoxyalkyl of 2 to 5 carbon atoms in the aggregate thereof, 10

R<sub>2</sub> is fluorine or chlorine, and

R<sub>3</sub> is alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 2 to 4 carbon atoms, alkoxyalkyl of 2 to 5 carbon atoms in the aggregate thereof, or alkenyl of 3 or 4 carbon atoms, with the proviso that when R<sub>3</sub> is methyl, R<sub>2</sub> is fluorine.

15 Alkyl in R<sub>1</sub> has preferably 1 to 2 carbon atoms.

The alkoxy moiety in alkoxyalkyl or the hydroxy moiety in hydroxyalkyl is preferably located in the terminal position of the alkylene chain which preferably has 2 or 3, especially 2, carbon atoms. The alkoxy radical in alkoxyalkyl is preferably methoxy. The double bond in alkenyl is in the 2,3 or 3,4-position. 15

20 Alkenyl is preferably allyl or 2-methyl-2-propenyl.

R<sub>1</sub> is preferably methyl. R<sub>3</sub> is preferably alkyl or alkoxyalkyl, especially alkyl. R<sub>3</sub> especially is methyl, ethyl or n-propyl.

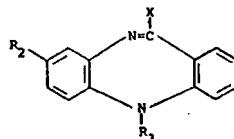
25 The present invention also provides a process for the production of a compound of formula I as defined above, which comprises reacting a compound of formula II,

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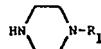
wherein

$R_2$  and  $R_3$  are as defined above, and

$X$  is a leaving group,

with a compound of formula III,

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III

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wherein

$R_1$  is as defined above.

The process may be effected in conventional manner for such reactions.

In the compound of formula II,  $X$  is attached by a covalent or ionic bond to the carbon atom, and signifies, for example, amino which may be substituted by one or two alkyl groups of 1 to 4 carbon atoms, especially 1 to 4 carbon atoms; sulphydryl, alkoxy or alkylthio of 1 to 4 carbon atoms, for example methoxy or methylthio, p-nitrobenzylthio or tosyloxy, or preferably halogen, especially chlorine.

The process is conveniently effected at temperatures between 50° to 170°C in an inert organic solvent, for example xylene or dioxane.

The starting materials of formula II may be prepared in known manner, e.g. as described herein, for example via the corresponding lactam, e.g. by reaction with phosphorusoxychloride.

Free base forms of compounds of formula I may be converted into the acid addition salt forms in conventional manner and vice versa. A suitable acid is hydrochloric acid.

In the following Examples all temperatures are in degrees Centigrade and are uncorrected.

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#### EXAMPLE 1

5-n-Propyl-8-chloro-11-(4-methyl-1-piperazinyl)-SH-dibenzo[b,e][1,4]diazepine

5.74 g of 5-n-propyl-8-chloro-10,11-dihydro-5H-dibenzo[b,e][1,4]diazepin-11-one, 30 ml of phosphorusoxychloride and 1 ml of N,N-dimethylaniline are boiled for 3 hours. The resulting solution of the imido-chloride of the lactam is evaporated to dryness, the residue evaporated twice more after the addition of xylene, and then boiled for 6 hours with 20 ml of dioxane and 25 ml of N-methylpiperazine. The resulting mixture is then concentrated as far as possible, and the residue is partitioned between aqueous ammonia and ether. The ethereal phase is washed with water, and extracted continuously with dilute acetic acid to remove the basic components. The base is set free by the addition of sodium hydroxide and taken up in chloroform. The chloroform phase is washed with water, dried over anhydrous sodium sulphate and concentrated to dryness. The residue is taken up in ether, filtered through basic aluminium oxide and crystallized from ether/petroleum ether to give the title compound; M.Pt. 120°—122°C.

The starting material may be obtained as follows:— 2-Nitro-4-chlorodiphenylamine-2'-carboxylic acid is converted via the acid chloride into 2-nitro-4-chloro-diphenylamine-2'-carboxylic acid methyl ester (M.Pt. 155°—156°). This is reacted with n-propyl iodide in the presence of sodium hydride in hexamethylphosphoric acid triamide to form N-n-propyl-2-nitro-4-chlorodiphenylamino-2'-carboxylic acid methyl ester. This is reduced in the presence of Raney nickel in ethyl acetate to form N-n-propyl-2-amino-4-chlorodiphenylamine-2'-carboxylic acid methyl ester. This is cyclized in the presence of sodium amide in boiling dioxane over several hours to yield the starting material used in Example 1.

In analogous manner to that described in Example 1, the following compounds of formula I may be obtained, wherein:—

Example	$R_2$	$R_1$	$R_3$	M.Pt.°	
55	2	Cl	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	145—146°
	3	Cl	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	160—161°
	4	F	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	133—135°
	5	F	CH <sub>3</sub>	n-C <sub>3</sub> H <sub>7</sub>	95—97° and 115—117°
	6	F	CH <sub>3</sub>	n-C <sub>4</sub> H <sub>9</sub>	124—125°
60	7	Cl	CH <sub>3</sub>	CH <sub>2</sub> —CH=CH <sub>2</sub>	157—159°
	8	Cl	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OH	157—159°

	9	Cl	CH <sub>3</sub>	iso-C <sub>3</sub> H <sub>7</sub>	152—154°	
	10	Cl	CH <sub>3</sub>	iso-C <sub>4</sub> H <sub>9</sub>	128—131°	
	11	Cl	CH <sub>3</sub>	n-C <sub>4</sub> H <sub>9</sub>	122—124°	
	12	F	CH <sub>3</sub>	CH <sub>3</sub>	172—174°	
5	13	F	CH <sub>2</sub> CH <sub>2</sub> OH	CH <sub>3</sub>	122—124°	5
	14	F	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	146—147°	
	15	F	H	CH <sub>3</sub>	147—149°	
	16	F	i-C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>	136—137°	
	17	F	n-C <sub>3</sub> H <sub>7</sub>	CH <sub>3</sub>	136—138°	
10	18	F	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	CH <sub>3</sub>	107—109°	10
	19	F	t-C <sub>4</sub> H <sub>9</sub>	CH <sub>3</sub>	170—171°	
	20	F	CH <sub>3</sub>	CH <sub>2</sub> —CH=CH <sub>2</sub>	139—140°	

The compounds of formula I exhibit pharmacological activity. In particular, the compounds of formula I exhibit neuroleptic activity as indicated by standard tests. For example, the compounds inhibit spontaneous locomotor activity in mice upon administration of from 1 to 50 mg/kg p.o. animal body weight of the compounds according to the principles of Caviezel et al Pharm. Acta Helv. (1958) 33, 469—484.

Additionally the compounds, wherein R<sub>2</sub> is chlorine and R<sub>3</sub> is alkyl or alkenyl, exhibit insignificant activity in tests indicating anti-cholinergic activity, e.g. in the mydriasis test and in tests indicating effects on blood circulation, e.g. in the infusion test in the cat.

Therefore the compounds are indicated for use as neuroleptics and the compounds of formula I, wherein R<sub>2</sub> is chlorine and R<sub>3</sub> is alkyl or alkenyl, exhibit surprisingly beneficial activity than is expected for such compounds.

An indicated daily dose is from about 10 to 500 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 2 to about 250 mg of the compound, or in sustained release form.

Compounds of formula I, wherein R<sub>2</sub> is fluorine, additionally exhibit anti-depressant activity, as indicated in standard tests. For example, these compounds inhibit the ptosis and catalepsy produced by tetrabenazine on i.p. administration of from 0.1 to 10 mg/kg animal body weight of the compounds to rats.

These compounds are therefore further indicated for use as anti-depressants. An indicated daily dose is from about 5 to about 150 mg, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 1 to about 35 mg of the compounds or in sustained release form.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of activity as the free base forms and are readily prepared in conventional manner. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be made in conventional manner so as to be, for example, a solution or a tablet.

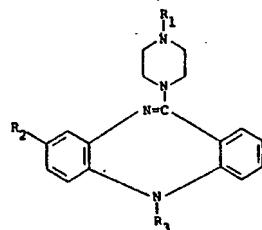
In one group of compounds R<sub>1</sub> is hydrogen, alkyl or hydroxyalkyl, and R<sub>3</sub> is hydroxyalkyl or alkoxyalkyl. In a sub-group R<sub>3</sub> is methoxyethyl, ethoxyethyl, propoxyethyl, ethoxypropyl, methoxypropyl or methoxybutyl.

In another group of compounds R<sub>1</sub> is alkyl and R<sub>2</sub> is chlorine, and R<sub>3</sub> is alkyl of 2 to 4 carbon atoms.

In another group of compounds R<sub>2</sub> is fluorine.

#### WHAT WE CLAIM IS:—

1. A process for the production of a compound of formula I,

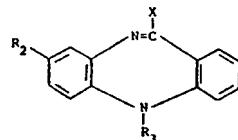


wherein

R<sub>1</sub> is hydrogen, alkyl of 1 to 4 carbon atoms, hydroxyalkyl of 2 to 4 carbon atoms, or alkoxyalkyl of 2 to 5 carbon atoms in the aggregate thereof,

R<sub>2</sub> is fluorine or chlorine, and

R<sub>3</sub> is alkyl of 1 to 4 carbon atoms, hydroxyalkyl or 2 to 4 carbon atoms, alkoxyalkyl of 2 to 5 carbon atoms in the aggregate thereof, or alkenyl of 3 or 4 carbon atoms, with the proviso that when R<sub>3</sub> is methyl, R<sub>2</sub> is fluorine, which comprises reacting a compound of formula II,



II

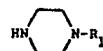
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wherein

R<sub>2</sub> and R<sub>3</sub> are as defined above, and

X is a leaving group,

with a compound of formula III,



III

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wherein

R<sub>1</sub> is as defined above.

2. A process for the production of a compound of formula I, as stated in Claim 1, substantially as hereinbefore described with reference to any one of the Examples.

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3. A compound of formula I, whenever produced by a process according to Claim 1 or 2.

4. A compound of formula I, as defined in Claim 1.

5. A compound of Claim 4, wherein R<sub>1</sub> is hydrogen, alkyl or hydroxyalkyl, and R<sub>3</sub> is hydroxyalkyl or alkoxyalkyl.

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6. A compound of Claim 4, wherein R<sub>1</sub> is alkyl, R<sub>2</sub> is chlorine and R<sub>3</sub> is alkyl of 2 to 4 carbon atoms.

7. A compound of Claim 4, wherein R<sub>2</sub> is fluorine.

8. A compound of Claim 4, which is 5-n-propyl-8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo[b,e][1,4]diazepine.

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9. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, Cl, C<sub>2</sub>H<sub>5</sub>.

10. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, Cl, CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>.

11. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, F, C<sub>2</sub>H<sub>5</sub>.

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12. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, F, n-C<sub>3</sub>H<sub>7</sub>.

13. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, F, n-C<sub>4</sub>H<sub>9</sub>.

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14. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, Cl, CH<sub>2</sub>=CH-CH<sub>2</sub>.

15. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, Cl, CH<sub>2</sub>CH<sub>2</sub>OH.

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16. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, Cl, iso-C<sub>3</sub>H<sub>7</sub>.

17. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, Cl, iso-C<sub>4</sub>H<sub>9</sub>.

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18. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, Cl, n-C<sub>4</sub>H<sub>9</sub>.

19. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, F, CH<sub>3</sub>.

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20. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>2</sub>CH<sub>2</sub>OH, F, CH<sub>3</sub>.

21. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively C<sub>2</sub>H<sub>5</sub>, F, CH<sub>2</sub>.

22. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively H, F, CH<sub>3</sub>.

23. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively i-C<sub>3</sub>H<sub>7</sub>, F, CH<sub>3</sub>.

24. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively n-C<sub>3</sub>H<sub>7</sub>, F, CH<sub>3</sub>.

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25. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>2</sub>CH<sub>2</sub>OCH<sub>3</sub>, F, CH<sub>3</sub>.

26. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively t-C<sub>4</sub>H<sub>9</sub>, F, CH<sub>3</sub>.

5 27. A compound of Claim 4, wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> are respectively CH<sub>3</sub>, F, CH<sub>2</sub>—CH=CH<sub>2</sub>.

28. A compound according to any one of Claims 3 to 27 in free base form.

29. A compound according to any one of Claims 3 to 27 in acid addition salt form.

10 30. A pharmaceutical composition comprising a compound according to any one of Claims 3 to 27 in free base form or in pharmaceutically acceptable acid addition salt form in association with a pharmaceutical carrier or diluent.

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